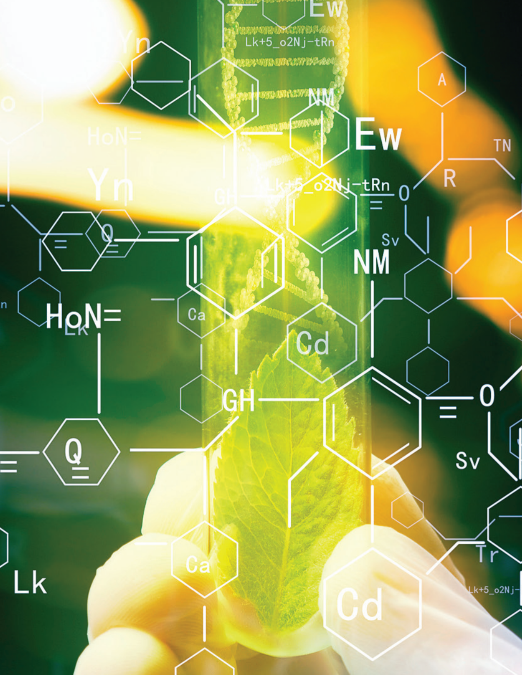


Clinical Development Success Rates 2006-2015

Bio Biotechnology Innovation Organization

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June 2016

About BIO

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology products. BIO also produces the BIO International Convention, the world's largest gathering of the biotechnology industry, along with industry-leading investor and partnering meetings held around the world.

About Biomedtracker

BioMedTracker, a subscription-based product of Informa, tracks the clinical development and regulatory history of investigational drugs to assess its Likelihood of Approval (LOA) by the FDA. BioMedTracker is populated in near real-time with updated information from press releases, corporate earnings calls, investor and medical meetings and numerous other sources.

About Amplion

Amplion is the leading biomarker business intelligence company, and its flagship product BiomarkerBase™, along with consulting services and free reports, deliver insights that inform key strategic decisions for drug and diagnostic test developers. Since 2012 Amplion has helped large and small companies alike make the best use of biomarkers in advancing precision therapeutics and next generation diagnostics. BiomarkerBase is a subscription-based service that tracks biomarker usage in clinical trials, drug labels, and tests (including laboratory-developed, FDA-cleared, and FDA-approved tests). BiomarkerBase is updated weekly with information from these sources and publications, using supervised machine learning algorithms for natural language processing (Amplion BiomarkerEngine) to identify biomarkers.

Executive Summary

This is the largest study of clinical drug development success rates to date. Over the last decade, 2006-2015, a total of 9,985 clinical and regulatory phase transitions were recorded and analyzed from 7,455 development programs, across 1,103 companies in the Biomedtracker database. Phase transitions occur when a drug candidate advances into the next phase of development or is suspended by the sponsor. By calculating the number of programs progressing to the next phase vs. the total number progressing and suspended, we assessed the success rate at each of the four phases of development: Phase I, II, III, and regulatory filing. Having phase-by-phase data in hand, we then compared groups of diseases, drug modalities and other attributes to generate the most comprehensive analysis yet of biopharmaceutical R&D success.

This work was made possible due to the years of clinical program monitoring and data entry by Informa's Biomedtracker service. BIO has long partnered with Biomedtracker to calculate success rates based on this data. More recently, BIO and Biomedtracker partnered with Amplion, the inventors of BiomarkerBase, to analyze the effects of biomarkers in clinical trial success.

Key takeaways:

- The overall likelihood of approval (LOA) from Phase I for all developmental candidates was 9.6%, and 11.9% for all indications outside of Oncology.
- Rare disease programs and programs that utilized selection biomarkers had higher success rates at each phase of development vs. the overall dataset.
- Chronic diseases with high populations had lower LOA from Phase I vs. the overall dataset.
- Of the 14 major disease areas, Hematology had the highest LOA from Phase I (26.1%) and Oncology had the lowest (5.1%).
- Sub-indication analysis within Oncology revealed hematological cancers had 2x higher LOA from Phase I than solid tumors.
- Oncology drugs had a 2x higher rate of first cycle approval than Psychiatric drugs, which had the lowest percent of first-cycle review approvals. Oncology drugs were also approved the fastest of all 14 disease areas.
- Phase II clinical programs continue to experience the lowest success rate of the four development phases, with only 30.7% of developmental candidates advancing to Phase III.

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Disease areas covered in this report:

- Allergy
- Autoimmune
- Cardiovascular
- Chronic High Prevalence Diseases
- Endocrine
- Gastroenterology
- Hematology
- Infectious Disease
- Metabolic
- Neurology
- Oncology
- Ophthalmology
- Psychiatry
- Rare Diseases
- Respiratory
- Urology

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Introduction

This study aimed to measure clinical development success rates to strengthen benchmarking metrics for drug development. To measure success rates for investigational drugs, we analyzed individual drug program phase transitions from January 1, 2006 to December 31, 2015. For the ten years studied, 9,985 transitions in the Biomedtracker database were analyzed. A phase transition is the movement out of a clinical phase – for example, advancing from Phase I to Phase II development, or being suspended after completion of Phase I development.

These transitions occurred in 7,455 clinical drug development programs, across 1,103 companies (both large and small), making this the largest study of its kind. With this broad set of data, we aimed to capture the diversity in drug development across levels of novelty, molecular modalities, and disease indications.

Only company-sponsored, FDA registration-enabling development programs were considered; investigator-sponsored studies were excluded from this analysis. A more detailed description of the data collection, composition, and analysis methodology are described at the end of this report under "Methods."

Individual Phase transition success rates were determined by dividing the number that advanced to the next phase by the total number advanced and suspended. This "advanced and suspended" number is often referred to as "n" in this report, and should be taken into account when drawing conclusions from the success rate results.

One of the key measures of success used in this report is the Likelihood of Approval (LOA) from Phase I. This LOA success rate is simply a multiplication of all four Phases success rates, a compounded probability calculation. For example, if each phase had a 50% chance of success, then the LOA from Phase I would be 0.5 x 0.5 x 0.5 x 0.5 = 6.25%.

Phase Transition Success and Likelihood of Approval (LOA) - Overall

Consistent with previous studies of drug development phase transition success rates, we found Phase II success rates to be far lower than any other phase.[1] Phase I and III rates were substantially higher than Phase II, with Phase I slightly higher than Phase III. The highest success rate of the four development phases was the NDA/BLA filing phase.

The Phase I transition success rate was 63.2% (n=3,582). As this Phase is typically conducted for safety testing and is not dependent on efficacy results for candidates to advance, it is common for this phase to have the highest success rate among the clinical phases across most categories analyzed in this report. Phase I success rates may also benefit from delayed reporting bias, as some larger companies may not deem failed Phase I programs as material and thereby not report them in the public domain. The Phase II transition success rate (30.7%, n=3,862) was substantially lower than Phase I, and the lowest of the four phases studied. As this is generally the first stage where proof-of-concept is deliberately tested in human subjects, Phase II consistently had the lowest success rate of all phases. This is also the point in development where industry must decide whether to pursue the large, expensive Phase III studies and may decide to terminate development for multiple reasons including commercial viability. The second-lowest phase transition success rate was found in Phase III (58.1%, n=1,491). This is significant as most company-sponsored Phase III trials are the longest and most expensive trials to conduct.

The probability of FDA approval after submitting a New Drug Application (NDA) or Biologic License Application (BLA), taking into account re-submissions, was 85.3% (n=1,050). Multiplying these individual phase components to obtain the compound probability of progressing from Phase I to U.S. FDA approval (LOA) reveals that only 9.6% (n=9,985) of drug development programs successfully make it to market (**Figure 1**).

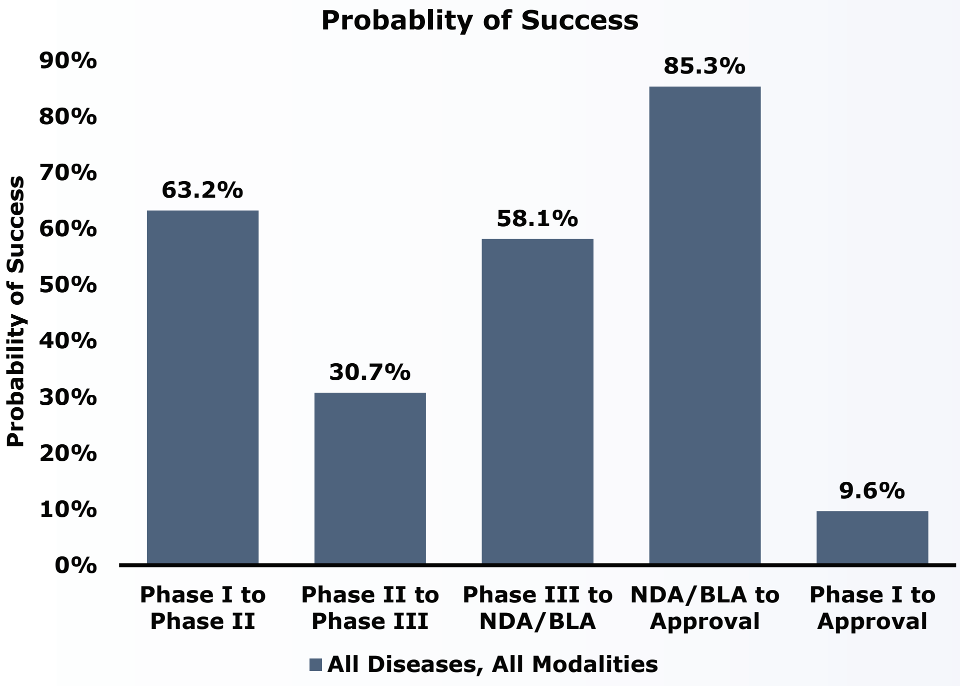


Figure 1. Phase transition success rates and LOA from Phase I for all diseases, all modalities.

Phase Transition Success and Likelihood of Approval (LOA) - by Disease

We segmented major disease areas according to the convention used by Biomedtracker, and categorized 21 major diseases and 558 indications for the 2006-2015 timeframe. For reporting at the disease area level, we analyzed only major diseases with more than 100 total transitions from Phase I to NDA/BLA approval. This resulted in 14 categorized disease areas: Allergy, Autoimmune, Cardiovascular, Endocrine, Hematology, Infectious disease, Gastroenterology (non-IBD), Metabolic, Neurology, Oncology, Ophthalmology, Psychiatry, Respiratory, and Urology. Disease areas with n <100 were placed into the "Other" category. This includes Dermatology, Renal, Obstetrics, Rheumatology (for non-autoimmune indications), Dental, and Orthopedics.

As can be seen in **Figures 2a**, there is a wide range of Likelihood of Approval (LOA) from Phase I. At the high end, Hematology towers over the other groups at 26.1% (n=283). A large portion of Hematology transitions came from Hemophilia, Anemia, and Blood Protein Deficiencies, Thrombocytopenia, and Hemostasis. Some of these Hemophilia indications had overall LOA that reached above 50%. This more than offset some of the weaker Hematology success rates that were observed in Venous Thromboembolism and Neutropenia. Hematology's LOA from Phase I was 5x the success rate for Oncology, which at 5.1% (n=3,163) had the lowest of all the major disease areas.

The next-highest LOA from Phase I under Hematology's 26.1% was Infectious Disease with an impressive 19.1% (n=916). Five disease areas follow closely in the 14-17% range: Ophthalmology > Other > Metabolic > Gastroenterology > Allergy. Below 14% there is a third group of diseases that was slightly above the overall average of 9.6%: Endocrine > Respiratory > Urology > Autoimmune. Falling under the overall LOA of 9.6% was a fourth group made up of four disease areas: Neurology > Cardiovascular > Psychiatry > Oncology. The fact that Oncology and Neurology had the two highest n values while also having low LOA values suggests that these two disease categories are a significant factor in bringing down the overall industry LOA.

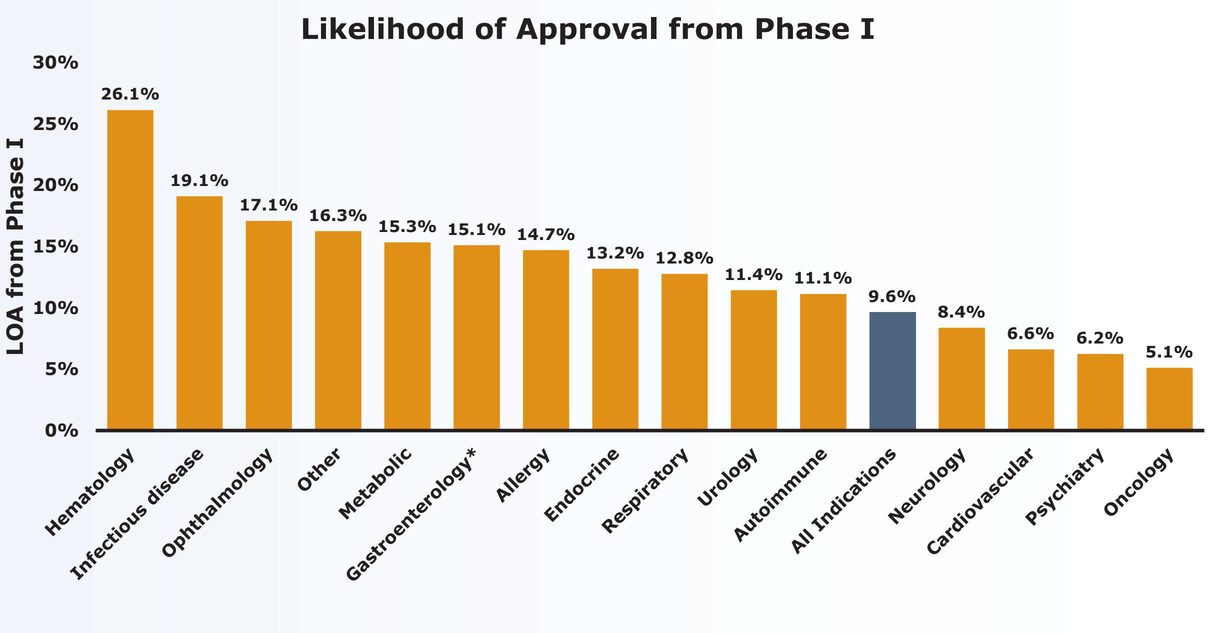


Figure 2a. Chart of LOA from Phase I, displayed highest to lowest by disease area.

Phase Success	Phase I to Phase II		Phase II to Phase III		Phase III to NDA/BLA		NDA/BLA to Approval	
	Advanced or Suspended	Phase Success	Advanced or Suspended	Phase Success	Advanced or Suspended	Phase Success	Advanced or Suspended	Phase Success
Hematology	86	73.3%	83	56.6%	64	75.0%	50	84.0%
Infectious disease	347	69.5%	286	42.7%	150	72.7%	133	88.7%
Ophthalmology	66	84.8%	101	44.6%	60	58.3%	40	77.5%
Other	96	66.7%	116	39.7%	46	69.6%	43	88.4%
Metabolic	95	61.1%	84	45.2%	35	71.4%	27	77.8%
Gastroenterology*	41	75.6%	56	35.7%	33	60.6%	26	92.3%
Allergy	37	67.6%	40	32.5%	14	71.4%	16	93.8%
Endocrine	299	58.9%	242	40.1%	143	65.0%	107	86.0%
Respiratory	150	65.3%	196	29.1%	45	71.1%	37	94.6%
Urology	21	57.1%	52	32.7%	21	71.4%	14	85.7%
Autoimmune	297	65.7%	319	31.7%	135	62.2%	86	86.0%
All Indications	**3582**	**63.2%**	**3862**	**30.7%**	**1491**	**58.1%**	**1050**	**85.3%**
Neurology	462	59.1%	465	29.7%	216	57.4%	161	83.2%
Cardiovascular	209	58.9%	237	24.1%	110	55.5%	76	84.2%
Psychiatry	154	53.9%	169	23.7%	70	55.7%	58	87.9%
Oncology	1222	62.8%	1416	24.6%	349	40.1%	176	82.4%

Likelihood of Approval	Phase I to Approval		Phase II to Approval		Phase III to Approval		NDA/BLA to Approval	
	LOA n	Phase LOA	LOA n	Phase LOA	LOA n	Phase LOA	LOA n	Phase LOA
Hematology	283	26.1%	197	35.7%	114	63.0%	50	84.0%
Infectious disease	916	19.1%	569	27.5%	283	64.5%	133	88.7%
Ophthalmology	267	17.1%	201	20.1%	100	45.2%	40	77.5%
Other	301	16.3%	205	24.4%	89	61.5%	43	88.4%
Metabolic	241	15.3%	146	25.1%	62	55.6%	27	77.8%
Gastroenterology*	156	15.1%	115	20.0%	59	55.9%	26	92.3%
Allergy	107	14.7%	70	21.8%	30	67.0%	16	93.8%
Endocrine	791	13.2%	492	22.4%	250	55.9%	107	86.0%
Respiratory	428	12.8%	278	19.6%	82	67.3%	37	94.6%
Urology	108	11.4%	87	20.0%	35	61.2%	14	85.7%
Autoimmune	837	11.1%	540	17.0%	221	53.5%	86	86.0%
All Indications	**9985**	**9.6%**	**6403**	**15.3%**	**2541**	**49.6%**	**1050**	**85.3%**
Neurology	1304	8.4%	842	14.2%	377	47.8%	161	83.2%
Cardiovascular	632	6.6%	423	11.2%	186	46.7%	76	84.2%
Psychiatry	451	6.2%	297	11.6%	128	49.0%	58	87.9%
Oncology	3163	5.1%	1941	8.1%	525	33.0%	176	82.4%

Figure 2b. Phase transition success and LOA by disease. Table of phase transition success and LOA by disease with corresponding n values. 'Advanced or Suspended' refers to the total number of transitions used to calculate each success rate, with the n value noted in the text. The LOA n value is the total 'Advanced or Suspended' transitions of all phases used to calculate LOA. 'Phase Success' is the probability of successfully advancing to the next phase, whereas 'Phase LOA' is the probability of FDA approval for drugs from this phase of development. *Gastroenterology does not include IBD.

Phase I Transition Success Rates by Disease

Success rates for Phase I ranged from 53.9% to 84.8%, with the average for all disease indications coming in at 63.2%. Looking at the distribution, we find that most disease area Phase I success rates cluster within +/-10% of the overall Phase I success rate. Two disease areas were outliers, and they are both to the upside. Ophthalmology registered an 84.8% (n=66) success rate, which was substantially higher (by >20%) than the overall Phase I success rate. Gastroenterology programs also exhibited an above average rate of successfully overcoming initial clinical safety hurdles with a 75.6% (n=41) Phase I success rate.

Phase II Transition Success Rates by Disease

In every disease area, Phase II had the lowest transition success rate of the four phases. As shown in **Figure 3**, Phase II success rates ranged from a high of 56.6% (Hematology, n=83) to a low of 23.7% (Psychiatry, n=169). Although it is widely known that drug program attrition is high in Phase II, it is interesting to find that the rate of success can vary by 33% among disease groups. The only Phase II success rate above 50% was seen in Hematology, which largely explains how that indication attained the highest LOA from Phase I.

Excluding Hematology, we can group the Phase II success rates into three clusters: success rates below the 30% overall success rate, those 31-36%, and those in the 40-45% range. Unlike what is observed in the LOA from Phase I, Oncology does not have the lowest success rate for Phase II. Cardiovascular and Psychiatry both registered slightly below the 25% success rate seen for Oncology.

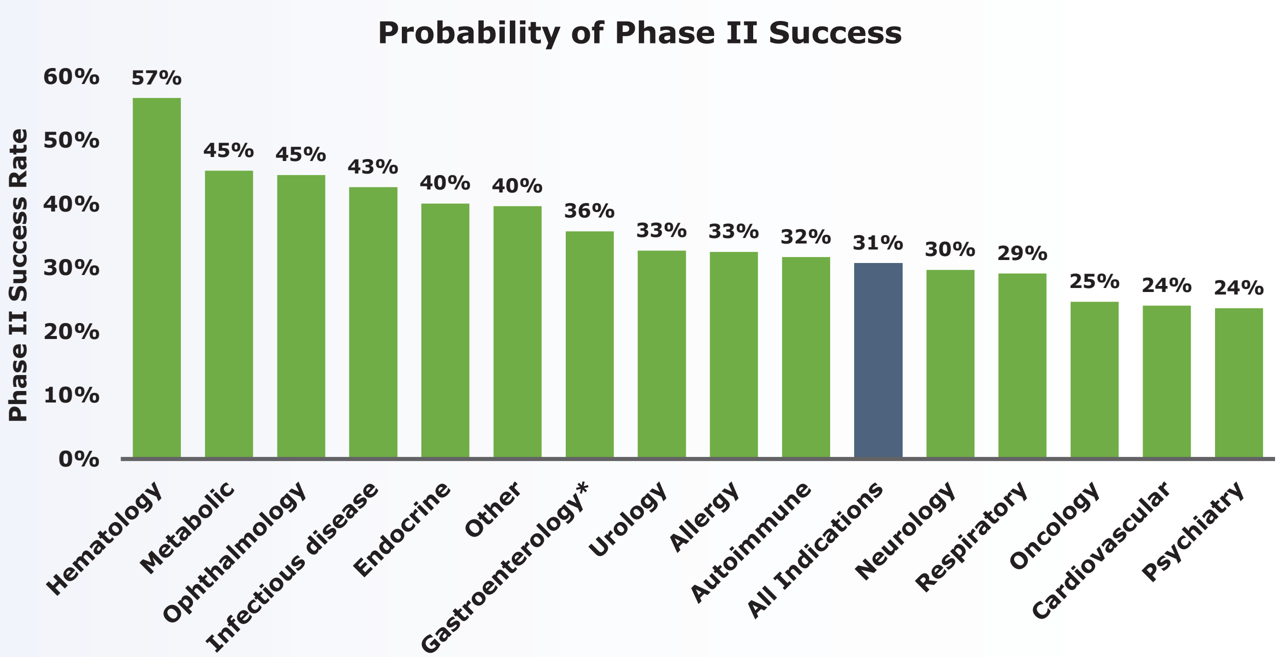


Figure 3. Phase II transition success rates by disease area. Categories are listed from highest to lowest based on the probability of transitioning from Phase II to Phase III. *Gastroenterology does not include IBD.

Phase III Transition Success Rates by Disease

For Phase III transition success rates, Oncology was the outlier with the lowest transition success rate. As seen in **Figure 4**, the Phase III success rates for 14 specific disease areas clustered into two ranges: near 70% and 55-65%. This places Oncology into a group of its own at just 40.1% (n=349).

In addition to Oncology, Neurology, Psychiatry and Cardiovascular were also below the overall Phase III success rate of 58.1% (n=1,491) at 57.4%, 55.7%, and 55.5%, respectively. Each of these areas included disease indications with large patient populations. Later in this report, we break down these high prevalence diseases and compare them with low prevalence disease areas.

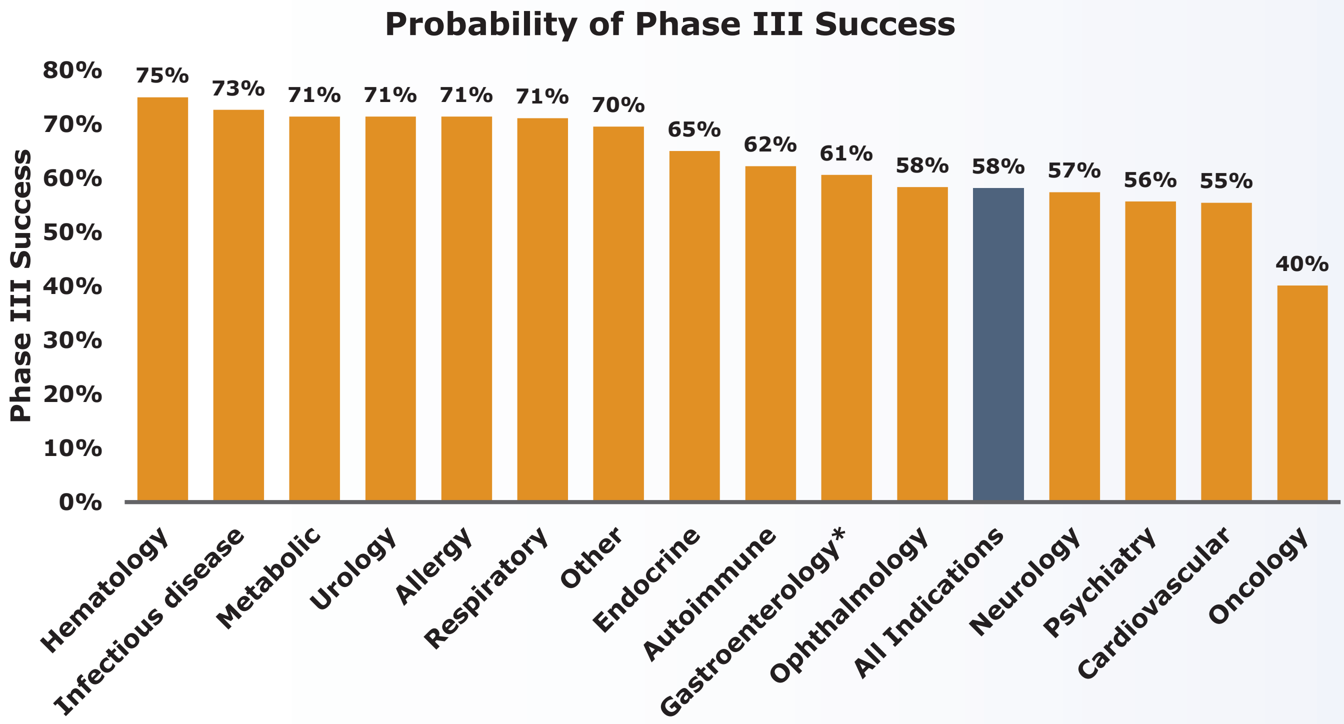


Figure 4. Phase III transition success rates by disease area. Categories are listed from highest to lowest based on the probability of transitioning from Phase II to NDA/BLA filing. *Gastroenterology does not include IBD.

NDA/BLA Submission Success Rates

NDA/BLA transition success rates (approval rates) for the disease areas listed in **Figure 2b** ranged from the low end of 77.5% (Ophthalmology) to a high of 94.6% (Respiratory). The distribution of rates (17.1%) were within the tightest range among the four phases analyzed in this report. These rates are the result of eventual success, not success on first review, meaning some programs may have as many as four Complete Response Letters (CRLs) and attempts at approval. This unrestricted time-frame and number of re-submissions pushes the overall success above 85% across all diseases.

When looking at how many original NDA/BLA filings were approved on the first review by FDA, the rates are far from concentrated (**Figure 5)**. In fact, Psychiatry had only a 37% chance of first-cycle approval vs. Oncology at nearly 80%. Although this is an extreme range, upon subsequent submissions and reviews, both of these disease areas ended up with 91% of original drug indication applications being approved. There was a large increase in cumulative success rates after the second submission, but only marginal increases after the third review.

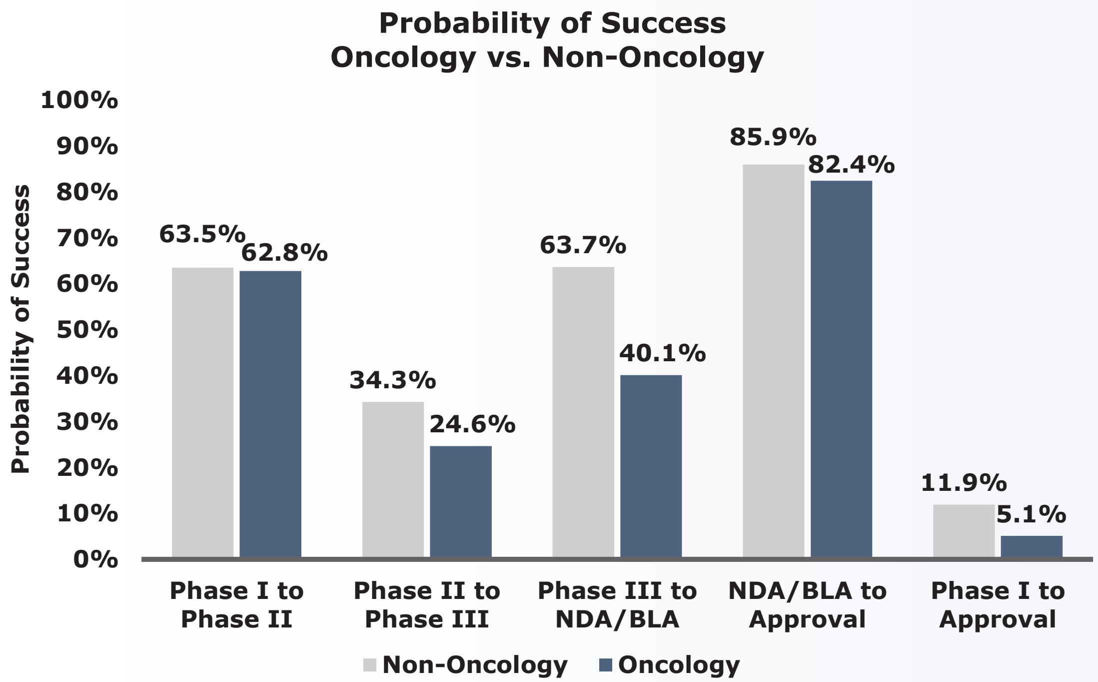
Time from filing to approval also varied by disease area. Neurology drugs took the longest to approve on average, at 2 years, while Oncology drugs were approved almost twice as fast at 1.1 years. Many Oncology drugs for unmet medical need may have benefited from expedited approval pathways and associated increased interactions with FDA such as Breakthrough Therapy and Accelerated Approval, contributing to the faster overall time to approval. As might be expected, calculating time to approval for all disease areas put the time to approval in the middle of these extremes, at 1.6 years.

Disease Area	% Approved on 1st Review	% Approved by 2nd Review	% Ultimately Approved	Filing to Approval Time (Years)
Oncology	79%	89%	89%	1.1
Allergy	71%	93%	93%	1.3
Respiratory	71%	94%	94%	1.6
Cardiovascular	69%	83%	85%	1.4
Infectious disease	69%	86%	92%	1.4
Urology	64%	73%	82%	1.7
Autoimmune	63%	82%	86%	1.6
Metabolic	63%	83%	83%	1.5
Ophthalmology	62%	69%	73%	1.3
All Diseases	61%	80%	86%	1.6
Hematology	60%	76%	90%	1.6
Gastroenterology	56%	84%	92%	1.8
Endocrine	56%	77%	83%	1.8
Neurology	45%	70%	81%	2.0
Psychiatry	37%	70%	91%	1.6

Figure 5. Time to FDA approval and percent approved by FDA for original NDA/BLA filings only. Data shown does not include supplemental applications.

Oncology and Non-Oncology Diseases

Oncology drug development program transitions in the 2006-2015 period accounted for 31% of the 9,985 total transitions. With the lowest LOA from Phase I (5.1%, n=3,163), Oncology had an outsized effect on the overall industry success rate. To further understand this contribution, we compared phase transition success rates and LOA for non-oncology development programs against oncology development programs alone. **Figure 6** shows Phase success rates and LOA from Phase I for oncology and non-oncology development programs. The LOA from Phase I across non-oncology indications was twice that for oncology alone, at 11.9% (n=6,822). Looking at individual phase transition success rates, it is clear that Phase III transition success rates were the reason Oncology ended up with the lowest overall success across our 14 disease categories. Oncology Phase III success was 23% lower than Non-Oncology disease areas.

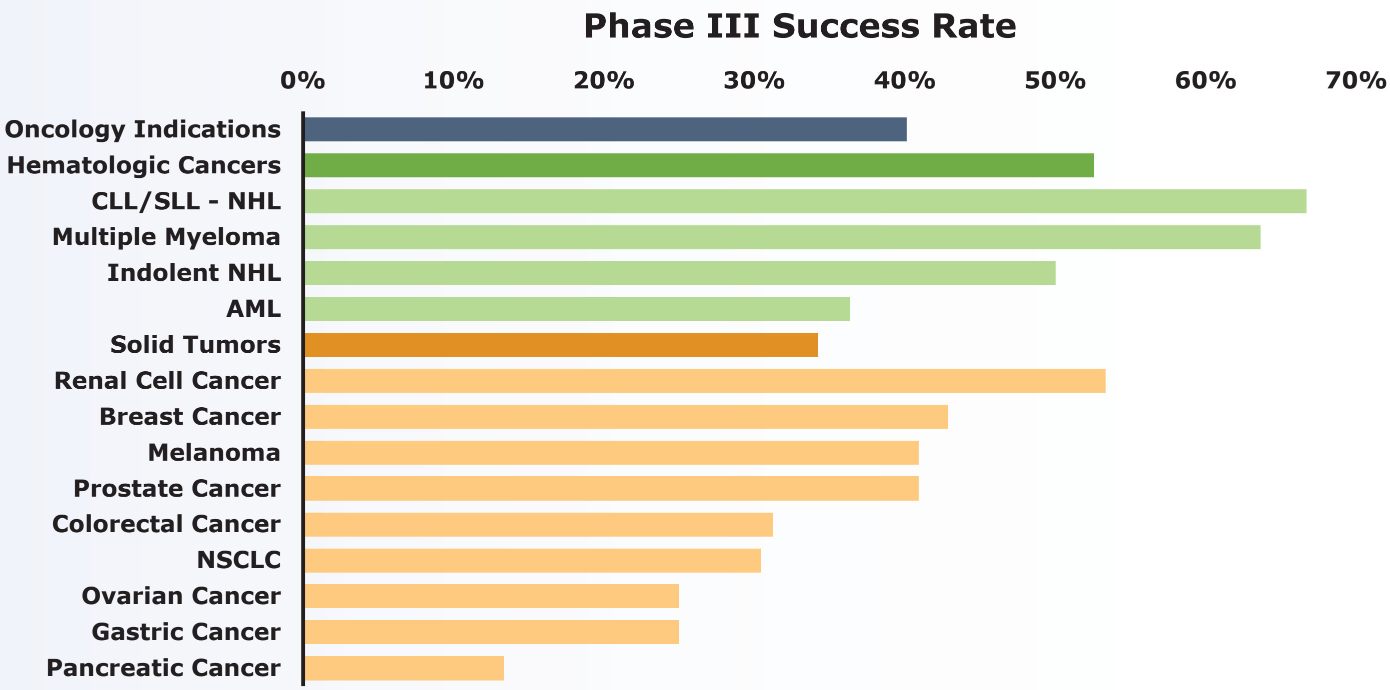


Phase Success	Phase I to Phase II		Phase II to Phase III		Phase III to NDA/BLA		NDA/BLA to Approval	
	Advanced or Suspended	Phase Success	Advanced or Suspended	Phase Success	Advanced or Suspended	Phase Success	Advanced or Suspended	Phase Success
Oncology	1222	62.8%	1416	24.6%	349	40.1%	176	82.4%
Non-Oncology	2360	63.5%	2446	34.3%	1142	63.7%	874	85.9%
Likelihood of Approval	**Phase I to Approval**		**Phase II to Approval**		**Phase III to Approval**		**NDA/BLA to Approval**	
	LOA n	Phase LOA	LOA n	Phase LOA	LOA n	Phase LOA	LOA n	Phase LOA
Oncology	3163	5.1%	1941	8.1%	525	33.0%	176	82.4%
Non-Oncology	6822	11.9%	4462	18.7%	2016	54.7%	874	85.9%

Figure 6. Oncology vs. Non-Oncology phase transition success rates and LOA. Top: Chart of LOA from Phase I. Bottom: Table of phase transition success rates and LOA for Oncology vs. Non-Oncology indications, with corresponding n values. 'Advanced or Suspended' refers to the total number of transitions used to calculate each success rate, with the n value noted in the text. The LOA n value is the total 'Advanced or Suspended' transitions of all phases used to calculate LOA. 'Phase Success' is the probability of successfully advancing to the next phase, whereas 'Phase LOA' is the probability of FDA approval for drugs in this phase of development.

Oncology Sub-Indication Phase Transition Success Rates and LOA

Oncology drugs were further categorized into two main types of cancer: solid tumors and hematological cancers. Solid tumors had twice as many transitions in the data set (2,283 vs. 805), but only half the LOA from Phase I vs. hematological cancers (4.0% vs. 8.1%). These are shown in **Figure 7** in more detail.



Phase Success	Phase I to Phase II		Phase II to Phase III		Phase III to NDA/BLA		NDA/BLA to Approval	
	Advanced or Suspended	Phase Success	Advanced or Suspended	Phase Success	Advanced or Suspended	Phase Success	Advanced or Suspended	Phase Success
Oncology	1222	62.8%	1416	24.6%	349	40.1%	176	82.4%
Solid	860	64.1%	1055	23.0%	260	34.2%	108	79.6%
Hematologic	327	61.8%	341	28.7%	78	52.6%	59	86.4%

Likelihood of Approval	Phase I to Approval		Phase II to Approval		Phase III to Approval		NDA/BLA to Approval	
	LOA n	Phase LOA	LOA n	Phase LOA	LOA n	Phase LOA	LOA n	Phase LOA
Oncology	3163	5.1%	1941	8.1%	525	33.0%	176	82.4%
Solid	2283	4.0%	1423	6.3%	368	27.3%	108	79.6%
Hematologic	805	8.1%	478	13.1%	137	45.4%	59	86.4%

Figure 7. Phase transition success rates and LOA for Oncology indications with corresponding n values. 'Advanced or Suspended' refers to the total number of transitions used to calculate each success rate, with the n value noted in the text. The LOA n value is the total 'Advanced or Suspended' transitions of all phases used to calculate LOA. 'Phase Success' is the probability of successfully advancing to the next phase, whereas 'Phase LOA' is the probability of FDA approval for drugs in this phase of development.

Phase II transition success rates by sub-indication tended to range close to the overall 25% Oncology calculation for Phase II, +/-10%.

Narrowing in on Phase III transition success rates, only 34.2% of the 260 drug programs in solid tumor cancers were deemed sufficiently successful to file an NDA/BLA with the FDA. This was the underlying cause for the 2x difference we see in overall LOA, as the hematological cancer programs recorded a 52.6% success rate in Phase III. Since Phase III was identified as the weakest phase for Oncology, Phase III transition success rates for a number of major oncology sub-indications were included in **Figure 7**.

The solid tumor Phase III transition success rate (34.2%, n=260) ended up as the lowest for any of the major disease categories studied. Solid tumor drugs for pancreatic cancer seemed to have the toughest challenges in Phase III studies (13.3%, n=15). However, Phase III success rates for Ovarian and Gastric cancers also fell below 30%.

Hematological cancer Phase III transition success rates benefited from transition successes in CLL/SLL (66.7%, n=12) and MM (63.7%, n=11). ALL, Hodgkin's and CML had Phase III success rates of 100% but only had fewer than five completed clinical development programs each (data not shown). Only AML (36.4%, n=11) came in below 40% for Phase III, which helped the overall hematologic cancer Phase III success rate remain above 50%.

The NDA/BLA to approval success rate for all hematological cancers (86.4%, n=59) was impacted positively by Multiple Myeloma, ALL, and CML success, as each had more than five completed filings and 100% approval rates. The NDA/BLA success rate for all sold tumors was lower at 79.6% (n=108).

Abbreviated cancer indications:

ALL - Acute Lymphocytic Leukemia

AML - Acute Myelogenous Leukemia

CLL - Chronic Lymphocytic Leukemia

CML - Chronic myelogenous Leukemia

MM - Multiple Myeloma

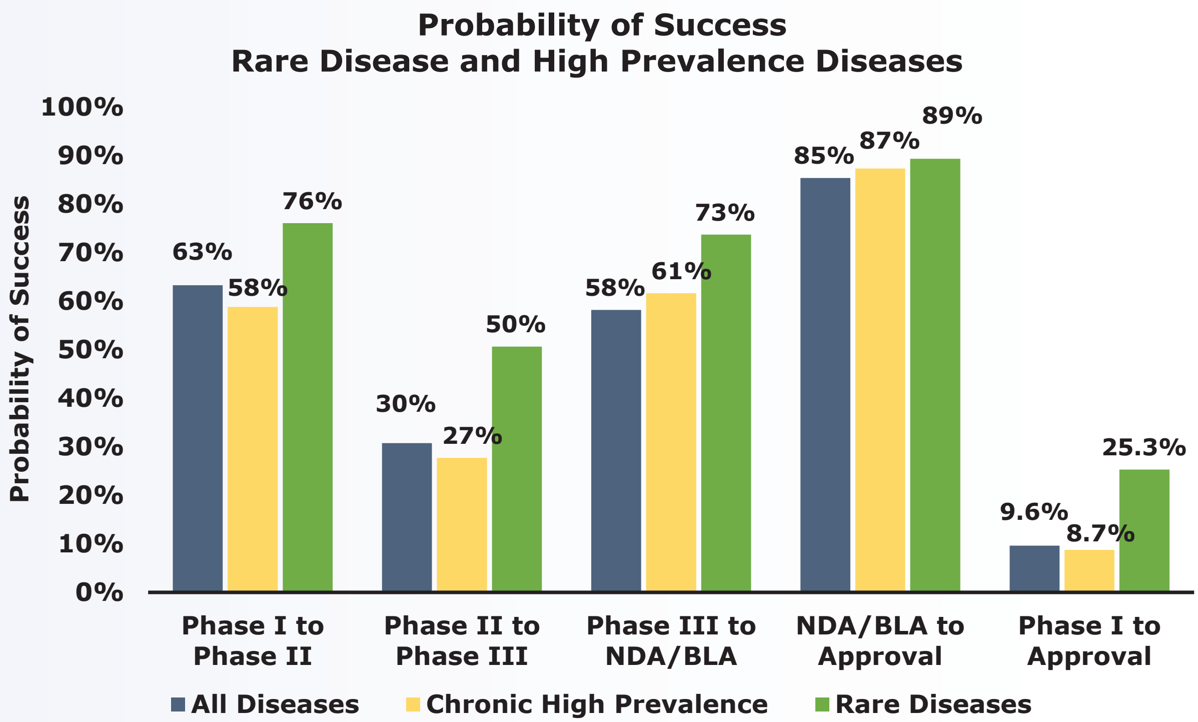
NHL - Non-Hodgkin's Lymphoma

NSCLC - Non-Small Cell Lung Cancer

SLL - Small Lymphocytic Lymphoma

Rare Diseases and Chronic High Prevalence Diseases

In recent years, there has been an increase in funding for companies focused on rare diseases.[2] This is welcome news as there are reportedly 7,000 rare diseases and most do not have an approved therapeutic treatment.[4] One question that is often asked is if the probabilities of success are any better for rare diseases, especially for those in which a particular defective gene has been confirmed as the sole contributor. On the other extreme, we have observed less venture funding for high prevalence, chronic diseases.[2] The question we wanted to explore is whether investors may have scaled back funding because there is a higher hurdle to developing and gaining approval for medicines that treat highly prevalent conditions.



Phase Success	Phase I to Phase II		Phase II to Phase III		Phase III to NDA/BLA		NDA/BLA to Approval	
	Advanced or Suspended	Phase Success	Advanced or Suspended	Phase Success	Advanced or Suspended	Phase Success	Advanced or Suspended	Phase Success
All Diseases	3582	63.2%	3862	30.7%	1491	58.1%	1050	85.3%
Chronic High Prevalence	732	58.7%	726	27.7%	268	61.6%	196	87.2%
Rare Diseases	150	76.0%	168	50.6%	110	73.6%	93	89.2%

Likelihood of Approval	Phase I to Approval		Phase II to Approval		Phase III to Approval		NDA/BLA to Approval	
	LOA n	Phase LOA	LOA n	Phase LOA	LOA n	Phase LOA	LOA n	Phase LOA
All Diseases	9985	9.6%	6403	15.3%	2541	49.6%	1050	85.3%
Chronic High Prevalence	1922	8.7%	1190	14.9%	464	53.7%	196	87.2%
Rare Diseases	521	25.3%	371	33.3%	203	65.7%	93	89.2%

Figure 8. Non-Oncology Rare disease and high prevalence, chronic disease. Top: Chart of phase transition success rates and LOA from Phase I, for rare and chronic, high prevalence. Bottom: Table of phase transition success and LOA by disease with corresponding n values. 'Advanced or Suspended' refers to the total number of transitions used to calculate each success rate, with the n value noted in the text. The LOA n value is the total 'Advanced or Suspended' transitions of all phases used to calculate LOA. 'Phase Success' is the probability of successfully advancing to the next phase, whereas 'Phase LOA' is the probability of FDA approval for drugs in this phase of development.

We isolated rare disease programs in the Biomedtracker database by first identifying all prior FDA Orphan-designated indications, then pooling all drug programs in these indications, regardless of whether they obtained FDA's Orphan designation. All Oncology indications were removed to make this rare disease analysis more concentrated on inborn genetic disorders. For chronic diseases, we first obtained a list of conditions from the Center for Medicare & Medicaid Services (CMS) Chronic Conditions Data Warehouse (CCW). We removed any cancer indications, then identified those disease with > 1 million patients afflicted with the disease in the United States.

With programs from both groups identified, we compared phase transition success rates and LOA as shown in **Figure 8**. At 25.3%, the overall LOA from Phase I for Non-Oncology rare diseases was 2.6x higher than the LOA for all diseases and 3x higher than the 8.7% LOA for chronic, high prevalence diseases. Chronic, high prevalence diseases accounted for almost 20% of the transitions, and Oncology, 31% of the transitions. The combined weighting of 50% of the dataset for these two categories with low LOAs (Chronic, high prevalence disease, 8.7% and Oncology, 5.7%) contributed significantly to the low overall industry LOA of 9.6%.

All four transition success rates were higher for the rare disease group than the overall dataset. The largest difference between was found in Phase II transition success rates (50.6% for rare disease vs 30.7% overall). Phase III and Phase I each had higher transition success rates by at least 10%.

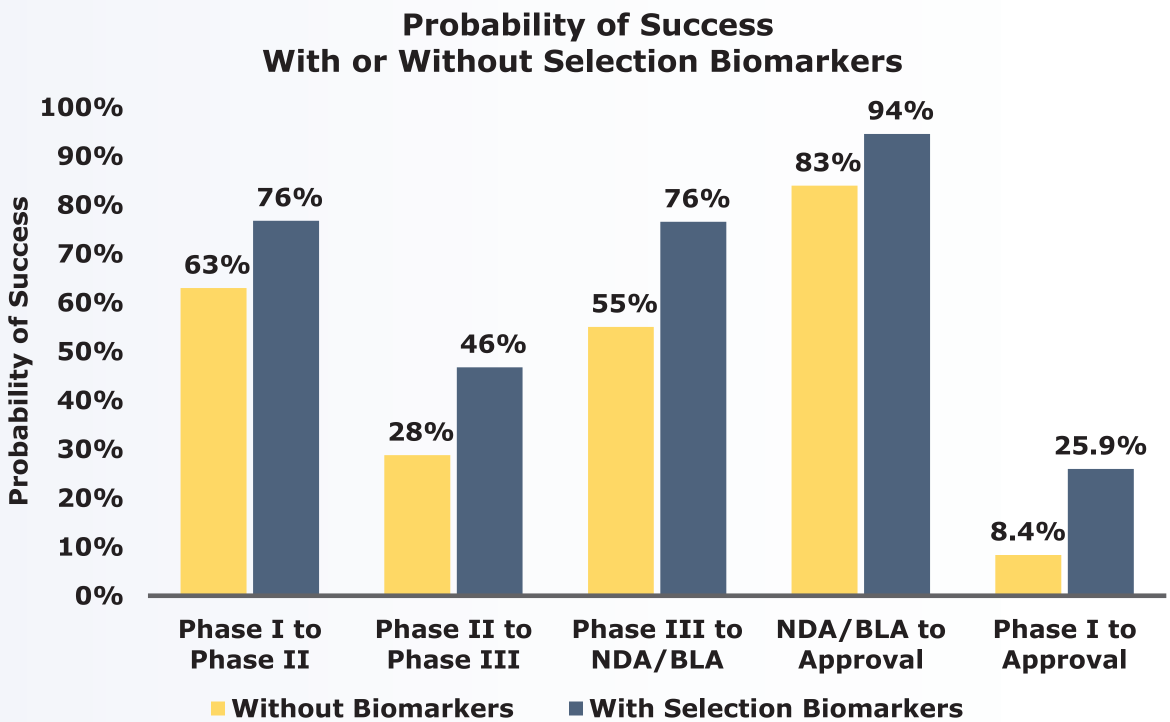
Chronic, high prevalence diseases transition success rates were lower in Phase I (58.7% vs 63.2%) and Phase II (27.7% vs. 30.7%) vs. the overall dataset. The opposite was seen in Phase III and NDA/BLA, where slightly higher rates were observed: 61.6% vs. 58.1% for Phase III and 87.2% vs. 85.3% for NDA/BLA.

As the chronic, high prevalence group in this study does not include Oncology, we compared these results with the Non-Oncology rates found in **Figure 6**. Although the chronic, high prevalence Phase III transition success rate is higher than that seen with all diseases, it is lower than the Non-Oncology transition success rates (61.6% vs. 63.7%). Furthermore, the LOA of 11.9% (n=6,822) for all Non-Oncology indications is 3% higher than for chronic, high prevalence diseases (8.7%), suggesting that these chronic indications are negatively impacting overall success rates outside Oncology.

Patient Selection Biomarker Programs

The use of biomarkers as inclusion or exclusion criteria, or 'selection biomarkers', for enrolling patients into clinical studies has increased dramatically since the sequencing of the human genome. We identified 512 phase transitions out of 9,985 (5%) that incorporated a selection biomarker for patient stratification. This was accomplished by mapping the NCT numbers (clinicaltrial.gov identifier) from Amplion's BiomarkerBase to programs in the Biomedtracker transition database.[6] For programs that filed an NDA/BLA, we only included filings that used selection biomarkers in the Phase III study design.

The LOA from Phase I can be found in **Figure 9**. The benefit from selection biomarker use raises the LOA from Phase I to one in four compared to less than one in 10 when no selection biomarker was used.



Phase Success	Phase I to Phase II		Phase II to Phase III		Phase III to NDA/BLA		NDA/BLA to Approval	
	Advanced or Suspended	Phase Success	Advanced or Suspended	Phase Success	Advanced or Suspended	Phase Success	Advanced or Suspended	Phase Success
No Biomarkers	3480	63.0%	3396	28.8%	1254	55.0%	882	83.9%
Selection Biomarkers	43	76.7%	246	46.7%	132	76.5%	91	94.5%
Likelihood of Approval	**Phase I to Approval**		**Phase II to Approval**		**Phase III to Approval**		**NDA/BLA to Approval**	
	LOA n	Phase LOA	LOA n	Phase LOA	LOA n	Phase LOA	LOA n	Phase LOA
No Biomarkers	9012	8.4%	5532	13.3%	2136	46.2%	882	83.9%
Selection Biomarkers	512	25.9%	469	33.8%	223	72.3%	91	94.5%

Figure 9. Selection Biomarker phase transition success rates and LOA. Top: Chart of individual phase transition success rates and LOA from Phase I for all indications without and with selection biomarkers. Bottom: Table of Phase transition success and LOA by disease with corresponding n values. 'Advanced or Suspended' refers to the total number of transitions used to calculate each success rate, with the n value noted in the text. The LOA n value is the total 'Advanced or Suspended' transitions of all phases used to calculate LOA. 'Phase Success' is the probability of successfully advancing to the next phase, whereas 'Phase LOA' is the probability of FDA approval for drugs in this phase of development.

As shown in the table of **Figure 9**, a three-fold higher LOA from Phase 1 was calculated for programs that utilized selection biomarkers (25.9%, n=512) vs. programs that did not (8.4%, n=9,012).

Individual phase transition success rates can be found in **Figure 9**. All four phase transition success rates were much higher for programs incorporating selection biomarkers vs. those not incorporating selection biomarkers. Phase III transition success rates for selection biomarker programs were 76.5% (n=132) vs. only 55.0% (n=1,254) for non-selection biomarker programs - the largest percentage difference among the four phases of development.

There were fewer completed Phase 1 trials that utilized a selection biomarker (43) than those observed in NDA/BLA filings (91). This is likely due to the fact that biomarkers are more commonly used in Phase II and III.

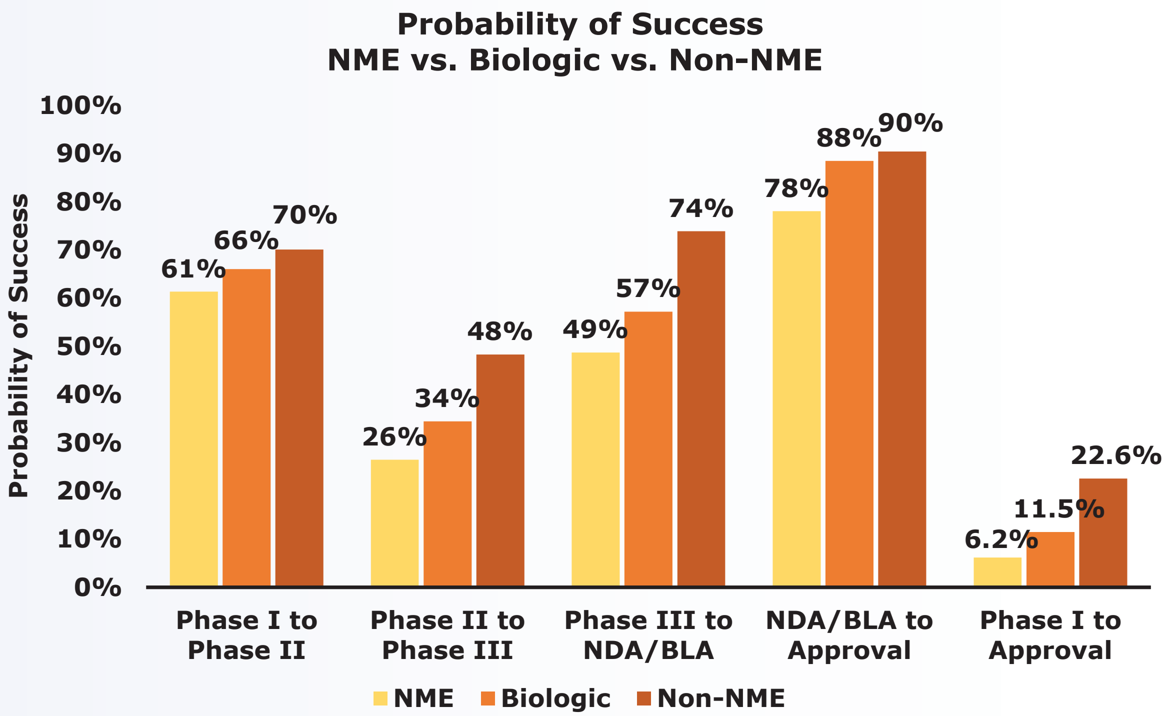
The large differences in Phase II and III transition success rates are quite convincing, quantitatively, of what many drug developers have long argued anecdotally – enrichment of patient enrollment at the molecular level is a more successful strategy than heterogeneous enrollment.

With respect to statistical rigor, while having a smaller number of transitions for programs that utilized a selection biomarker (512) vs. for non-biomarker phase transitions (9,012), when analyzed for statistical significance, all phases, save for Phase I, were found to be statistically significant. This is in large part due to the low n value for Phase I, a clinical phase in which few selection biomarkers are actually used.

Drug Classification and Modality

Drugs in the dataset were annotated by: new molecular entity (NME), non-NME, biologic and vaccine.

Most NMEs are small molecules, although in some cases FDA will designate larger molecules, such as proteins and peptides, as NMEs. When comparing small-molecule NMEs to all NMEs we found very little difference in success rates. The Non-NME classification often includes drugs with the same molecular properties as NMEs, but are frequently reformulations or combinations of approved products. Non-NMEs often use the 505(b)(2) pathway to gain FDA approval. Monoclonal antibodies made up the majority of biologics in the dataset. Other biologics in the dataset included gene therapy, cell therapy, RNAi, and other large molecules. Generic and over-the-counter (OTC) drugs were not included.



Phase Success	Phase I to Phase II		Phase II to Phase III		Phase III to NDA/BLA		NDA/BLA to Approval	
	Advanced or Suspended	Phase Success	Advanced or Suspended	Phase Success	Advanced or Suspended	Phase Success	Advanced or Suspended	Phase Success
NME	2236	61.3%	2482	26.5%	731	48.7%	409	78.0%
Biologic	882	66.0%	883	34.4%	313	57.2%	199	88.4%
Non-NME	314	70.1%	406	48.3%	398	73.9%	406	90.4%
Vaccine	95	66.3%	76	32.9%	35	74.3%	32	100.0%
Likelihood of Approval	**Phase I to Approval**		**Phase II to Approval**		**Phase III to Approval**		**NDA/BLA to Approval**	
	LOA n	Phase LOA	LOA n	Phase LOA	LOA n	Phase LOA	LOA n	Phase LOA
NME	5858	6.2%	3622	10.1%	1140	38.0%	409	78.0%
Biologic	2277	11.5%	1395	17.4%	512	50.6%	199	88.4%
Non-NME	1524	22.6%	1210	32.2%	804	66.8%	406	90.4%
Vaccine	238	16.2%	143	24.4%	67	74.3%	32	100.0%

Figure 10. Phase transition success rates and LOA by drug type and class. Top: Chart of phase transition success rates and LOA from Phase I by FDA classification for NME, Biologic, Non-NME. Bottom: Table of phase transition success rates and LOAs for FDA's classifications and vaccines. 'Advanced or Suspended' refers to the total number of transitions used to calculate each success rate, with the n value noted in the text. The LOA n value is the total 'Advanced or Suspended' transitions of all phases used to calculate LOA. 'Phase Success' is the probability of successfully advancing to the next phase, whereas 'Phase LOA' is the probability of FDA approval for drugs in this phase of development.

NMEs were found to have the lowest transition success rates in every phase of development and an LOA from Phase I of just 6.2% (n=5,858). Biologics had almost 2x this LOA (11.6%, n=2,277), as shown in **Figure 10**. The breakout of Monoclonal Antibodies yielded the exact same 11.6% LOA from Phase I (n= 1,258).

Non-NMEs had the highest LOA from Phase I of 22.6% (n=1,524), with transition success rates well above the NME and biologic classifications in every phase. However, many non-NMEs begin development in Phase II or Phase III, so the actual approval rate is likely higher (assuming that successful Phase I outcomes would contribute positively to the LOA from Phase I).

Although a much smaller subset of the modality breakout, vaccines generated a healthy 16.1% (n=238) LOA from Phase I.

Discussion

During the time frame of this study (2006-2015), programs entering clinical development in Phase I were found to have only a one in ten (9.6%) chance of advancing all the way to FDA approval. Although this is an overall probability calculation and does not follow each program from its first trial to final outcome (which is often be outside of a 10-year time-frame), we believe that these low success rates for individual drug programs accurately reflect overall industry realities. This is particularly important in the context of cost and time of unsuccessful clinical trials.

Potential factors that may have impacted success rates in this report include:

Clinical and regulatory related:

- Patient population and selection strategy. The impact that a targeted, well-defined patient population can have was observed in the success rates for both selection biomarker usage and rare disease studies.
- Clinical validation of a target, drug class, or mechanism of action. Note that non-NME drugs presented in this report are drugs developed for already approved classes and targets and have 3x higher LOA from Phase I vs. novel NMEs.
- Clinical trial complexity. In chronic, high prevalence diseases, where large heterogeneous patient populations will be treated, additional safety and efficacy studies may be required. These areas have experienced below average LOA from Phase I.

Corporate related:

- Lack of funding. This is a common issue for emerging companies, especially during times of economic stress such as in the years following the global financial of 2008. Programs terminated due to lack of resources or funding would be counted as "suspended" in this study and not differentiated from programs terminated based on disappointing clinical data.
- Commercial decisions and portfolio prioritization. Competition, IP litigation, and other market factors could result in the termination of a program. Internal programs at companies may also compete during pipeline review and prioritization, potentially leading to program termination.

The overall low rates for Phase III programs to successfully transition to an NDA/BLA filing is concerning, as 35% of all R&D spending is now spent on Phase III development, and Phase III trials account for 60% of all clinical trial costs.[3] A main contributor to the overall low Phase III transition success rate was found to be Oncology clinical programs. While Oncology remains a very challenging area in which to develop drugs, some more recent successes in immunotherapies give hope that there will be highly successful drug programs in Oncology in coming years.

Outside of Oncology, clinical programs targeting heterogeneous patient populations in chronic, high prevalence indications also contributed to lower overall success rates. For this group, all three clinical-stage transition success rates were lower than the Non-Oncology disease group.

As selection biomarkers are used more frequently in clinical development (presently, they are only being used in a small proportion of studies), phase transition success rates in high prevalence diseases should improve as patient selection improves. The higher success rates for trials run with biomarker-selected patients suggests that the broader industry is already on the right path. For example, Phase III transition success rates in programs utilizing selection biomarkers in the last decade were 76.5% (n=132) compared to only 55.0% (n=1,254) for non-biomarker trials. Experiencing one in four failures (with selection biomarkers) vs. two in four Phase III failures (without biomarkers) could have significant cost implications.

As many rare diseases are identified by specific genetic mutations, it is not surprising that success rates in rare disease indications closely match the success rates observed in clinical trials that utilized selection biomarkers. Phase transition success rates for rare disease candidates and candidates utilizing selection biomarkers were very similar for every stage of development. Transition success rates for each classification, rare disease programs and programs with selection biomarkers, respectively, were; Phase I: 76% and 76.7%; Phase II: 50.6% and 46.7%; Phase III: 73.6% and 76.5%; and NDA/BLA: 89.2% and 94.5%. Both of these specific classifications significantly outpaced the success rates seen for chronic, high prevalence disease drug development at 58.7% in Phase I, 27.7% in Phase II, 61.6% in Phase III, and 87.2% in the NDA/BLA stage.

Greater flexibility with alternative and novel surrogate endpoints, the utilization of adaptive clinical trial design, improved methodologies for assessing patient benefit-risk, and improvements in communication between sponsors and regulators could help improve the success rates reported in this study. Simultaneously, improvements in basic science can enable better success rates. For example, more predictive animal models, earlier toxicology evaluation, biomarker identification and new targeted delivery technologies may increase future success in the clinic.

Advancing industry-wide understanding of the evidentiary standards or considerations governing regulatory acceptance of drug development tools including biomarkers would increase adoption and use of innovative drug development tools, and serve to expedite development and review timelines and improve chances of success.

The ability to utilize these modern approaches to drug development and modern regulatory review processes combined with healthy capital markets supporting private-sector investment will enable biopharmaceutical companies to develop the next generation of innovative medicines.

Methods

Drug Development Programs analyzed in this report track a specific indication for each drug. For example, Rituxan in non-Hodgkin's lymphoma (NHL) qualifies as a different development path than Rituxan in multiple sclerosis (MS). Biomedtracker assigns a unique internal identifier which can be used to isolate all development paths.

In addition to tracking the phase of development, Biomedtracker also assigns "lead" status to certain development paths. This is used to denote the most advanced indication in clinical development for a specific drug. Drugs can only have one lead development program (with some rare exceptions). For example, cancer drugs developed in multiple indications will have the most advanced program assigned as the lead, and the rest as "non-lead". However, in this report we do not differentiate the most advanced programs, and analyze the data on a program/development path level, which more accurately reflects company resource utilization.

Individual Phase Transition Success Rates were calculated as the number of drugs that moved from one phase to the next phase divided by the sum of the number of drugs that progressed to the next phase and the number of drugs that were suspended. The n value associated with the phase transition success rates represent the number of drugs that have advanced plus the number of drugs that have been suspended, which we label as phase transitions. Phase transition Success rates reported in this study were based on transition rates, not necessarily resulting from safety or efficacy data. Transition rates are negatively impacted by early development termination due to commercial and regulatory uncertainty as well as economic and portfolio management decisions.

Biomedtracker further classifies events by phase of development, summarized in the table below:

Biomedtracker phase	Description for purposes of the study
I	Drug is currently in Phase I
I/II, II, IIb	Drug is currently in Phase II
II/III, III	Drug is currently in Phase III
NDA/BLA	Application for approval has been submitted to the FDA and is currently under review
Approved, Withdrawn From Market, Approved (Generic Competition)	Drug has been approved for marketing in the United States
Suspended	Drug is no longer in development
Approved in Europe, Approved in other than U.S./E.U., Development, Development Outside U.S.	The company developing this drug does not plan to market it in the United States

Generic products were not included, but generic manufacturers developing novel investigational drugs were represented.

Likelihood of Approval (LOA) denotes the probability of reaching FDA approval from the current phase, and is also expressed as a percentage. LOA is calculated as the product of each Phase Success probability leading to FDA approval. The n value associated with LOA is the sum of the n values for each Phase Success included in the LOA calculation.

For example, if a drug is currently in Phase II, and the phase success for Phase II is 50% (n=10), Phase III is 50% (n=10), and FDA Approval is 50% (n=10), then the LOA for the Phase II drug would be 12.5% (50%×50%×50%=12.5%, n=30).

Data Source for Drug Program Transitions. Data used for this study were extracted from Biomedtracker using a Probability of Technical Success (PTS) tool, which identified all 'Advanced' and 'Suspended' drugs by development phase from January 1, 2006 to December 31, 2015. Biomedtracker, a subscription-based product of Informa, tracks the clinical development and regulatory history of investigational drugs to assess their Likelihood of Approval (LOA) by the FDA. Biomedtracker is populated in near real-time with updated information from press releases, corporate earnings calls, investor and medical meetings and numerous other sources. These data are recorded in BioMedTracker and tagged with a date. BioMedTracker also uses other sources, including regular communication with companies conducting clinical trials, to ensure accuracy and timeliness of the data.

Drug Classification Methods. Biomedtracker records FDA classification (i.e. new molecular entity (NME), non-NME, biologic, or vaccine) as well as the biochemical profile (e.g. small molecule, monoclonal antibody, peptides, natural proteins, antisense, vaccine, etc.). Biologics, as defined by FDA, can be sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues.

Sub-Indications. Drilling down into sub-indications within each major disease area has limitations due to lower n values for each phase. The statistical significance of the results must be taken into account when comparing data from low sample sizes. Although this study is over a 10-year period, some sub-indications had a limited number of Phase III programs completed or NDA/BLA filings submitted. For example, because AML had four drugs submitted for FDA approval, and no wins, the success rate for AML at the NDA/BLA stage is 0% (n=4). That also means that the LOA calculation for AML yields 0% (n=103), due to the compounded approach of multiplying individual phase probabilities to arrive at the overall LOA. With that caveat in mind, it is best to approach sub-indications starting with the NDA/BLA filing phase to assess n values and % success.

Data Source for Selection Biomarkers. Selection biomarkers are gene products used as inclusion or exclusion criteria for enrolling patients into clinical studies. The biomarker subject selection data used for this study were extracted from BiomarkerBase, which identifies selection biomarkers described in clinical trials posted at ClinicalTrials.gov. BiomarkerBase is a subscription-based service from Amplion that tracks selection biomarker usage in clinical trials, drug labels, and tests (including laboratory-developed, FDA-cleared, and FDA-approved tests). BiomarkerBase is updated weekly with information from these sources and publications, using supervised machine learning algorithms for natural language processing (Amplion BiomarkerEngine) to identify selection biomarkers. BiomarkerBase includes primarily human genes and proteins. Other diagnostic measurements, including clinical blood chemistry, liver enzymes, white blood cell count, heart rate, blood oxygenation, blood glucose, clotting times, etc. are not included in BiomarkerBase.

Comparison with Previous BIO/Biomedtracker Study. The Biomedtracker database has expanded since our original publication in Nature Biotechnology, January 2014.[1] The first study contained 5,820 phase transitions from 2003-2011. The current study contains 9,985 transitions from 2006-2015 (10 years). This more recent finding for overall LOA success rates falls within the same statistical range as our previous report (near 10.4%, n=5,820 for 2003-2011).[1,2] While the more recent study captures four additional years (2012-2015), it begins in 2006 and thus cuts 2003-2005 data, leaving a 10-year window for evaluation. Importantly, there are 4,165 more transitions in the current dataset. Such broad sample size comparisons makes it very difficult for significant changes to be found in overall rates. To see significant change would require more than just a few disease areas to experience profound improvements in productivity. For example, the impressive success rates found in Hematology might need to be seen in the larger groups such as Oncology or Neurology to move the needle. Narrowing the time-frame to detect improvements, can lead to program biases as R&D timelines are typically closer to a 10-year time-frame and not less.

Lead Drug vs. Non-Lead. In our previous report, we had included “Lead” drug success rates.[1] That allows us to answer the question: “What is the probability that a drug will reach approval for *any* indication?” However, the Lead program analysis will not represent the true costs, both monetary and time, that is required for approval. Furthermore, it can be a source of confusion in that it refers not to a company’s lead program, but rather the most advanced indication for a given drug. Lead indication status is constantly changing within the database through time as programs fail and secondary indication then become the Lead indication. For this reason, the current study focuses on each development path to answer the question: “What is the probability that a drug developed for a *specific* indication will reach approval?”

For those interested in the Lead indication success rates, the overall Lead success rate was 16.8% (n = 5,511), 1.7x higher than the 9.6% reported for individual development paths. This is a slightly wider difference than our previous finding (for 2003-2011) of 15.3% for the Lead indication. As the spread between Lead and subsequent individual indication programs widens, it could be argued that more R&D is required (across multiple indications) to reach final approval of a chemical entity in at least one of its indications.

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